Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

August 27, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Ln., Rm. 1061
Rockville, MD 20852

Re: [Docket No. 99D-1454] Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation (Published in Federal Register: June 2, 1999)

Dear Madam or Sir:

Eli Lilly and Company is pleased to have the opportunity to provide comments on the Draft Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation.

We commend the FDA and the Division of Pulmonary Drug Products for developing the Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Guidance and recognize the hard work by CDER that was necessary in producing such a comprehensive document. There are some issues upon which we wish to comment. We hope that these comments will result in revisions that will make the guidance more user friendly and compatible with FDAMA and ICH guidances. We would encourage the FDA to utilize a forum for industry inputs prior to issuing draft guidances.

To facilitate FDA review, our attached comments are divided into two parts: (1) a list of our general concerns, and (2) a table which describes specific technical points that we wish to make.

Please feel free to contact me at (3 17) 276-0368, or Mary Barbara Miller at (3 17) 277-7894 for clarification of any comments.

Sincerely,

Tobias Massa, Ph.D.
Director, Global Regulatory Affairs
Chemistry Manufacturing and Control

99D-1454

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Lilly Response to FDA Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products CM&C Documentation Draft Guidance

GENERAL CONCERNS

1. For clarity, the guidance should have a separate section for “Devices”, rather than blend into Drug Product sections. We suggest that the immediate container for the drug product should be described under the section “Container and Closure Systems” and that a separate section of the submission is set up to describe the device portion of the combination product. According to the 1991 Inter-Center Agreement between CDER and CDRH, the device component of the combination product will be reviewed and regulated according to the device authorities (i.e., the device laws and regulations). Arrangement of the information in this way could also facilitate easier consultation with device experts in CDRH when necessary for a product review.

   Note that existing CDRH guidances may not be applicable to these types of inhalation combination products. A separate CDRH guidance is needed for these types of inhalation combination products.

   It is recommended to separate the guidance document into 3 major sections, Drug, Device, and Integrated System.

2. In general, too much detail is provided in specification guidance. Development science should drive the specifications, not a “one-size-fits all” approach. Specification limits should be the scientifically driven result of a combination of
   - the limits used for the material used in actual safety and efficacy studies, and
   - the results from those safety and efficacy studies

3. Testing that should be done during product development as part of product characterization for the to-be-marketed drug product does not need to be on routine testing. Once a drug product is in final form, for example, further testing of leachables and extractables is redundant.

4. Refer to USP/ICH when applicable rather than create separate standards. This minimizes updating requirements. Specify any special aspects of these types of products that would require standards beyond ICH/USP, and provide examples or references for understanding.

Lilly Response to FDA Draft Guidance: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products CMC Documentation

Technical Points				
Index	**Line**	**Issue**	**Change to**	**Rationale**
IIA.	57-58	"The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product." Section III. B. of a related draft FDA Guidance: "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" states: "Similarly, nasal sprays consist of the formulation, container, pump, actuator, protection cap and protective packaging, which together constitute the drug product."	Need consistent definition of nasal spray drug product between CMC and ADME guidances.	Consistent definition of terms.
II. C.	111-114	"If such changes are made subsequent to the preparation of the batches used in critical clinical... studies, adequate supportive comparative data should be provided to demonstrate equivalency.. ."	Add: "Additionally, generic drug applicants must therefore provide adequate supportive comparative data to demonstrate equivalency in terms of Chemistry, Manufacturing and Control to the innovator drug."	Draft guidance appears to assert that the final formulation and device must be used by innovator firms during critical clinical trials. If this is so, then generic drugs and devices must also be demonstrated to be identical to the innovator drug. Need to clarify what comparative data are required—physico-chemical and/or safety and efficacy.
[II. B. DP Composition, [II.E. DP Method(s) of Manufacture and Packaging	144-145, 313	"excesses should be included.. .", "formulation *overfill* per container.. ."	Clarify "excesses and "overfill" and define in Glossary. Excess (also called overcharge in industry) is to compensate for manufacturing losses. Overfill is to compensate for retention of the drug product the container.	
[II.B. **Drug** Product Composition	149-157	"The composition of suspension formulations.. ."	Clarify: Provide data/references to support this assertion.	Throughout this draft Guidance, possible problem areas for product development are mentioned but no data nor references are cited to provide examples.
.II.C. I. DP Specifications	175	microbial limits (10 g sample size, USP<61>)	Smaller sample size (less than 10 g) may be used when justified (e.g. for protein Drug Substance)	It will clarify the requirement.

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III.C.1. DP Specifications	192-203	"The purity of the drug substance and its impurity profile..."	The purity of the drug substance and its impurity profile should be evaluated according to ICH Guidelines Q3A Impurities in New Drug Substances and Q3C Impurities: Residual Solvents.	Consistency with ICH.
III.C.2. Excipients	211	"Because of the sensitive nature of the patient population "	Proper product development warrants that...	The patient population and product indications are assumed.
III.C.2. Excipients	211-212	"excipients used in oral inhalation drug products:	excipients used in inhalation solution, suspension and spray drug products	Consistent use of definition of product form as per the Glossary of Terms.
III.D. Manufacturers	284-285	"Excipient manufacturers should be identified by name and address."	Manufacturers of non-compendial excipients should be identified by name and address.	Such information can be waived if the excipient is a USP or NF monograph materials
III.E. Method(s) of Manufacture and Packaging	304-306	A copy of the actual (executed) batch record and in-process controls should be filed, as appropriate, for representative submitted batches (e.g., clinical, biobatch, primary stability, production).	Specify this requirement for the Third Copy (Field Copy) and not for the general description of the method of manufacture and packaging.	Reference is made to CFR 314.50 (d)(ii)(c) which states that a comparably detailed description of the production process for a representative batch of the drug product is sufficient. Should not have unique CMC requirement for this product.
III.E. Method(s) of Manufacture and Packaging	289-338	No discussion of reprocessing operations.	Create a section stating reprocessing requirements..	
III.E Method(s) of Manufacture and Packaging.	330	"For inhalation drug products..."	For inhalation solution, suspension and spray drug products.. .	Consistent use of definition of product form as per the Glossary of Terms
III.F. Specifications for the Drug Product	342-345	"A complete description of the acceptance criteria and analytical procedures with analytical sampling plans should be provided.. ."	Delete references to analytical sampling plans.	Sampling plans are outside purview of CDER. In a letter (signed by Dr. Janet Woodcock for CDER and Dr. Ronald Chesemore for ORA, received Oct. 14, 1994) to clarify roles between CDER and ORA, it states: "The field investigator will be responsible for determining the adequacy of the storage system controls, sampling controls. "

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III.F.1.a. Nasal Sprays Appearance, Color and Clarity	364-367 AND 603-607	" then a quantitative test with appropriate acceptance criteria should be established for the drug product."	This work is done at the development stage and should not be included in the routine quality control for lot release. Explicit visual inspection should be sufficient.	If the process is validated in the development stage, the burden of QC can be reduced
III.F.1.d. Nasal Sprays Impurities and Degradation Products	392-393 AND 619-622	"All related impurities appearing at levels of 0.1 percent or greater should be specified."	See ICH guideline Q3B, Impurities in New Drug Products for the requirements for the identification and qualification of impurities.	Consistency with ICH
III.F.1.f. Nasal Sprays Pump Delivery	410-413 AND 671-673	Pump spray weight delivery...target weight.	Clarify that a solution representative of the formulation may be used for this testing as an alternative to the actual formulation.	
III.F.1. Nasal Sprays	435-447, AND 458-474	Detailed specification limits are not appropriate in this level of guidance.	State key concerns for each parameter (what/why to control), rather than explicit limits and let product development define control specifications.	Specifications should be based on product development data and history on a case by case basis.
III.F.1.i. Nasal Sprays Spray Pattern and Plume Geometry	478-502	The document recommends that spray pattern testing be performed on a routine basis for release testing. The need for spray pattern testmg for routine release is not obvious.. During routine manufacturing, control of the defined tolerances/specifications for the device parameters should be sufficient without the need to introduce a complex test such as spray pattern in routine testing. Additionally, the document recommends acceptance criteria include shape and size requirements.	Spray patterns for the formulation should be characterized during development and impact of device parameters (nozzle size/shape, pump characteristics, etc) on the spray pattern established leading to definition of tolerances for critical device parameters	Have already evaluated pump SCU. What is the medical relevance of spray pattern and plume geometry? Recommend these tests be a simple, qualitative limit test rather than requiring determination of shape and size.

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III.F. 1.l. Nasal Sprays Microscopic Evaluations (Suspensions)	527-536	For nasal suspension products, microscopic evaluation is being recommended for both release and stability testing. However, the need for microscopic testing should be considered on a case by case basis and not mandated for all suspension nasal products	The microscopy test is useful as complementary to particle size measurement during development to monitor for any changes in morphology, crystal growth, etc. Based on the data collected during development (including, if needed, primary stability batches), it should be possible to define appropriate control strategy without the need to transfer a qualitative/semi quantitative method such as the microscopic method to the QC labs. There may be some cases of complex suspension products where subtle changes in size/morphology (which may not be readily picked up in particle size measurement) may occur which can significantly affect bioavailability. In such specific cases, the need for some microscopic evaluation during routine manufacturing may be justified.	The cited examples are items that should be identified and characterized in product development and should be controlled by other means. This technique is useful and appropriate as a development tool; however, the value of the technique as a control tool is limited by the subjectivity of the technique. Drawbacks include drift in subjective evaluations and difficulty in establishing suitable standards, controls, and limits.
III.F. 1.m. Foreign Particulates	538-544 AND 637-640	Non-USP terminology "foreign particulates"	Clarify intent of this section.	Terminology is unclear. Foreign substances = introduced by contamination or adulteration USP <1081>. Particulate matter and Foreign matter <USP1> do not apply to non-sterile products, Already control impurities and microbial limits in **sections** d. and n.

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III.F.1.q. Leachables (Stability)	580-591	"The drug product should be evaluated for compounds that leach from elastomeric or plastic components of the container closure system.. .	Characterization of leachates should follow accepted procedures outlined in the USP including testing with the drug product matrix.	In general, the proposed studies to evaluate leachables are excessive without clearly establishing the need on a specific basis. The need for any extensive leachable testing (including during stability) by determination of specific extractables should be clearly based on the extraction potential of the formulation (cosolvents, high/low pH, surfactant, etc). For the majority of the products covered in this guideline (which are likely to be aqueous based), the potential for the formulation to leach extractables from device components can be evaluated as part of compatibility studies during the development phase . The need to identify specific extractables (by methods such as GC, LC/MS, etc) may only bc needed if an extractable constituent becomes apparent during these studies.
	827	" The identity and concentration of the leachables in the drug product or placebo formulation.. . through the end of the drug product shelf life should be determined".		
	891-902	"The purpose of the control extraction studies.. .appropriate organic solvents."		Regarding controlled extraction studies to establish the extraction profiles on all critical components: Such studies may be of limited value & relevance and also establishing acceptance criterion for such tests are likely to be difficult. The leachable section of the guideline needs further review to ensure that the significant work it is likely to entail are relevant and only conducted where specifically required (and not as a general requirement). Following pharmacopcial guidance will provide a uniform approach to leachate identification and characterization

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III.F.1.q. Leachables (Stability)	587-588	"These validated procedures can, in turn, be used for testing of the drug product throughout the expiration dating period."	Delete this sentence.	Stability studies of leachables should only be required during product development. Once a final drug product is registered, routine stability studies of leachables should not be required.
IIIF.2.s. Particle/Droplet Size Distribution for Inhalation Sprays	779	Aerodynamic particle /droplet size distribution (Line 779): For inhalation solutions, suspensions and sprays, the guideline recommends the use of a second particle size measurement technique such as light scattering or time-of-flight as complementary to the aerodynamic size measurement utilizing the multistage cascade impactor.	The need for the use of a second particle size measurement should be clearly based on cases where the particle/droplet size distribution are unique for the drug product and cannot be characterized by cascade impaction alone and not as a general requirement	The need for particle size measurement by two techniques for routine release will add to time/cost with no obvious added control.
III.G. Container Closure Systems	818-820	"If the device includes electronic components...refer to ...guidances from (CDRH)."	Delete reference to CDRH guidance. Include specific guidance for these types of products here. OR, Retain reference here and create a separate CDRH guidance for these types of inhalation combination products.	Current CDRH guidance is not applicable for these types of products. Need a separate CDRH guidance for these types of inhalation combination products. For ex. The electronic components section of the current CDRH guidance requires a drip test. Need to implement agreements from the Combination Products guidelines.
III.G.3. Routine extraction	931-933 AND 964-966	"An extraction test should be performed on every incoming component batch.. ."	Extraction profile should be characterized during development and only repeated if there are changes in the formulation or composition of components. Routine testing is unnecessary.	Extraction studies should only be required during product development. Once suppliers are qualified and a final drug product is registered, routine testing of extractibles should not be required.
III.H.1.d.Stability Test Storage Conditions	1048-1055	There is no reference to refrigerated storage conditions.	Acknowledge refrigerated storage conditions.	It will clarify the requirement for refrigerated products
III.H.1.e. Batches, Mfg. Process, Facilities, Components, etc.	1080-1083	The three batches should be prepared from the formulation and container closure system components intended for marketing, which should be the same as those used in submitted batches (e.g. clinical, biobatch, primary stability, production).	It is unclear what the 3 batches denoted. Delete the "primary stability" from the examples.	It appears that the 3 batches here are referenced to the 3 primary stability lots. Therefore, it will be clearer if they are not referenced again in the examples.

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III.H. 2. Other Stability Considerations	1141-1145	If multiple manufacturing facilities, manufacturing processes, or sources of the components (container and closure or formulation) are intended to be used in the manufacturing of the drug product, adequate stability data should be generated from each different facility, process, or source.	Stability requirements should be consistent with FDAMA and ICH guidelines.	FDAMA states that "a drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility". In addition, the ICH guideline does not require site specific stability data for registration. It is only necessary to demonstrate that the product is stable at time of registration. If the pivotal stability lots are made in the same equipment in kind, and by the same process that will be used commercially, then the only site specific data needed are validation dam. Further, validation data are required only prior to marketing a product, not for NDA approval. It is the manufacturer's responsibility to assure validation is performed in a timely manner to allow marketing soon after approval. In current practice, validation protocols only are required at the PAI. The FDA will have the commercial stability protocol available in the application and the company will commit to placing the first three commercial batches into the stability program according to this protocol, as per ICH guidance. Additional concerns about site specific stability data have been documented in the PhRMA position paper which was sent on 9/26/1997 to Roger L. Williams. MD, by Mr. Thomas X. White.

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IV. 0. Drug Product Characterization Studies: Stability of Primary (unprotected) Package	1318-1319	"…adequate stability data conducted at a minimum of 25 degrees C and 40% RH.. ."	For any case where ICH is inadequate, for example, refrigerated conditions, please delineate FDA expectations.	

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